

Huber & Schüßler · Truderinger Straße 246 · 81825 München  
Europäisches Patentamt  
80298 München

Truderinger Straße 246  
D-81825 München  
Tel.: \*\*49.89.437788-0  
Fax: \*\*49.89.43778899  
[munich@huber-schuessler.info](mailto:munich@huber-schuessler.info)  
[www.huber-schuessler.com](http://www.huber-schuessler.com)

Dr. Bernard Huber  
Dipl.-Biologe  
Dr. Andrea Schüßler  
Dipl.-Chemikerin

In Zusammenarbeit mit  
Rechtsanwälten  
Dr. Wolfram Städtler  
Stephan Biagosch

February 27, 2004

File No.: PCT/EP03/03928  
Applicant: Affimed  
Our Ref: A 3054 - sch / tz

**In response to the written opinion dated November 28, 2003**

Substantive examination of the present PCT application is requested.

**1. Novelty**

The claims are novel over the cited prior art.

S. KIPRIYANOV ET AL. describes a number of bispecific antibodies with a specificity to human CD19 or CD30 on lymphoma cells as well as to CD3 or CD28 or CD16 on T or NK effector cells. This document does not disclose the specific claimed combination of two different bispecific antibodies, wherein the first antibody recruits T-cells and the second antibody recruits CD3-epsilon negative effector cells.

T. KUDO ET AL. describes antibodies of different specificities potentially useful for tumor therapy. This paper does not disclose using antibody combinations recrui-

HypoVereinsbank München  
(BLZ 700 202 70)  
4 410 221 220  
IBAN  
DE 34 7002 0270 4410 2212 20  
SWIFT (BIC): HYVEDEMMXXX

Deutsche Bank München  
(BLZ 700 700 24)  
4 362 000  
IBAN  
DE 85 7007 0024 0436 2000 00  
SWIFT (BIC): DEUTDEDGMUC

ting different subsets of human effector cells as claimed. All antibodies described in this publication are targeting T-LAK cells against tumor cells.

C. RENNER ET AL. describe the combined use of CD30xCD3 and CD30xCD28 bispecific antibodies. However, both of them are binding T-cells (CD3 epsilon positive cells). Thus, this publication does not disclose to recruit CD3-epsilon negative effector cells as required by claim 1(d).

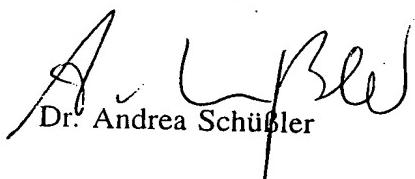
L. DA COSTA ET AL. describe CD30xCD3 and CD30xCD28 bispecific antibodies recruiting T-cells and also CD30xCD16 antibodies retargeting NK cells. However, no hint on using them in combination is given.

## 2. Inventive Step

The present invention is based on the finding that two different bispecific molecules recruiting different populations of defined effector cells, i.e. T-cells and CD3-epsilon negative cells, to the same tumor target show a significant synergistic therapeutic effect. Example 5 demonstrates that the treatment of SCID mice bearing an established Burkitt's lymphoma with CD19xCD16 and CD19xCD3 results in the complete elimination of tumors in 80% of animals. Such a significant synergistic effect could neither be derived nor expected from the prior art. Hence, the subject-matters of the claims are not obvious.

A favorable International Preliminary Examination Report (IPER) is expected. However, if novelty and/or inventive step cannot be acknowledged, we herewith request for drawing up a second written opinion before the International Preliminary Examination Report is established.

Patent Attorney



Dr. Andrea Schüßler

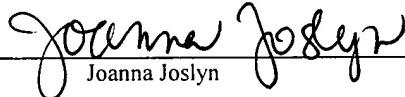
10/510881

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

<b>In re United States Patent Application of:</b>	) Docket No.: 4121-172
<b>Applicant(s):</b> Kipriyanov, et al	) Examiner: Not Yet Assigned
<b>Application No.:</b> New U.S. National Stage Application of PCT International Application No. PCT/EP03/03928	) Art Unit: Not Yet Assigned
<b>Int'l Filing Date:</b> 15 April 2003	) Customer No.:
<b>Priority Date:</b> 19 April 2002(European Patent Application No. 02008845.6)	) <div style="border: 1px solid black; padding: 5px; text-align: center;">23448</div>
<b>Title:</b> ANTIBODY COMBINATION USEFUL FOR TUMOR THERAPY	)

## EXPRESS MAIL CERTIFICATE

I hereby certify that I am mailing the attached documents to the Commissioner for Patents on the date specified, in an envelope addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 and Express Mailed under the provisions of 37 CFR 1.10.


\_\_\_\_\_  
October 8, 2004\_\_\_\_\_  
Date\_\_\_\_\_  
EO 002 820 255 US\_\_\_\_\_  
Express Mail Label Number

---

**SUBMISSION UNDER 35 U.S.C. §371 OF UNITED STATES PATENT APPLICATION  
(NATIONAL PHASE PROCEEDINGS) BASED ON INTERNATIONAL APPLICATION NO.  
PCT/EP03/03928 AND CLAIMING PRIORITY OF EUROPEAN PATENT APPLICATION NO.  
02008845.6**

---

Mail Stop PCT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

10/510881

DT04 R PCT/PTO 08 OCT 2004

Submitted herewith for filing under the provisions of 37 CFR §1.53 and 35 U.S.C. §371 is the above-referenced patent application, based on International Patent Application No. PCT/EP03/03928 and claiming priority of European Patent Application No. 02008845.6. A copy of the PCT International application and related documents as originally filed are also included. Further included is a Preliminary Amendment, unsigned Declaration and Power of Attorney, return postcard, a check in the amount of \$556.00, and 35 U.S.C. §371 transmittal forms.

Please direct correspondence relating to this application to Steven J. Hultquist, Intellectual Property Technology Law, P.O. Box 14329, Research Triangle Park, NC 27709, and direct telephonic communications relating to this application to Marianne Fuierer at (919) 419-9350.

Respectfully submitted,



Marianne Fuierer  
Registration No. 39,983  
Attorney for Applicants

**INTELLECTUAL PROPERTY/  
TECHNOLOGY LAW**  
P.O. Box 14329  
Research Triangle Park, NC 27709  
Tel: (919) 419-9350  
Fax: (919) 419-9354  
Attorney Ref.: 4121-172

FORM PTO-1390		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>				4121-172
				U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
				<b>10/510881</b>
INTERNATIONAL APPLICATION NO.		INTERNATIONAL FILING DATE		PRIORITY DATE CLAIMED
PCT/EP03/03928		15 April 2003		19 April 2002
TITLE OF INVENTION <b>ANTIBODY COMBINATION USEFUL FOR TUMOR THERAPY</b>				
APPLICANT(S) FOR DO/EO/US <b>KIPRIYANOV, Sergey; LE GALL, Fabrice; COCHLOVIUS, Björn and LITTLE, Melvyn</b>				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</li> <li>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).*(<b>Unsigned</b>)</li> <li>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol>				
<b>Items 11. to 16. below concern other document(s) or information included:</b>				
<ol style="list-style-type: none"> <li>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>14. <input type="checkbox"/> A substitute specification.</li> <li>15. <input checked="" type="checkbox"/> Small entity status is claimed.</li> <li>16. <input type="checkbox"/> Other items or information:</li> </ol>				

10/510881

				CALCULATIONS	PTO USE ONLY
				DT04 Rec'd PCT/PTO 08 OCT 2004	
17. <input checked="" type="checkbox"/> The following fees are submitted: <b>Basic National Fee</b> (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO ..... \$950.00					
International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... \$750.00 No International preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... \$790.00					
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$1110.00					
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... \$100.00					
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				\$ 950.00	
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	29 - 20 =	9	X \$18.00	\$ 162.00	
Independent Claims	3 - 3 =	0	X \$88.00	\$ 0	
Multiple dependent claim(s) (if applicable)				+ \$300.00	\$
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>1112.00</b>	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
<b>SUBTOTAL =</b>				<b>\$ 556.00</b>	
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 Months from the earliest claimed priority date (37 CFR 1.492(f)). +				\$	
<b>TOTAL NATIONAL FEE =</b>				<b>\$ 556.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +				\$	
<b>TOTAL FEE ENCLOSED =</b>				<b>\$ 556.00</b>	
				<b>Amount to be:</b>	\$
				<b>refunded</b>	
				<b>Charged</b>	\$

- a.  A check in the amount of **\$556.00** to cover the above fees is enclosed.
- b.  Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c.  The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **08-3284**. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not yet been met, a petition to revive (37 CFR 1.127(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

Steven J. Hultquist  
 Intellectual Property/Technology Law  
 P. O. Box 14329  
 Research Triangle Park, NC 27709

  
 Marianne Fuierer  
 Registration No. 39,983